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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,979	CAROZZI ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 1/3/07

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19 and 22-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,19 and 22-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 May 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-11, 19 and 22-36 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The drawings filed 12 May 2006 are objected to for inclusion of new matter. In the originally filed drawings, the protein alignments are different. Applicant is required to remove all instances of new matter that have been introduced into the drawings. Additionally, the description of Fig 1 and 2 in the paragraph on pg 4 discusses amino acids that are highlighted in black and gray, but such highlighting is not present in the drawing.

4. The rejection of claim 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention is withdrawn in light of Applicant's amendment of the claim.

Claim Objections

5. Claims 1, 26 and 29 are objected to because "and" is missing at the end of part (c).

Claim Rejections - 35 USC § 112

6. Claims 1-11, 19 and 22-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:3 and 5, host cells, plants, plant cells and seeds comprising them, and method of using them to make SEQ ID NO: 3and 5, does not reasonably provide enablement for nucleic acids encoding SEQ ID NO:7, nucleic acids encoding pesticidal protein with 90% identity to SEQ ID NO:3, 5 or 7, nucleic

acids with 90% identity to SEQ ID NO:1, 2, 4, or 6, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 90% identity to SEQ ID NO:3, 5 or 7 and a pesticidal protein encoded by a nucleic acid with 90% identity to SEQ ID NO:1, 2, 4 or 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the rejection set forth in the Office action mailed 25 July 2006, as applied to claims 1-11, 19 and 22-25. Applicant's arguments filed 3 January 2007 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding a pesticidal protein with 90% identity to SEQ ID NO:3, 5 or 7, nucleic acids with 90% identity to SEQ ID NO:1, 2, 4 or 6, or a complement of those nucleic acids, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 90% identity to SEQ ID NO:3, 5 or 7 and a pesticidal protein encoded by a nucleic acid with 90% identity to SEQ ID NO:1, 2, 4 or 6.

The instant specification, however, only discusses sequencing of DNAs from non-publically available bacterial strain ATX13026 (examples 1-4), identification of a nucleic acid, SEQ ID NO:1, that encodes a protein, SEQ ID NO:3, with 66% identity to the delta endotoxin cry40Aa, and an alternate start site variant, SEQ ID NO:4, which encodes SEQ ID NO:5 (examples 5-6), identification of an open reading frame, SEQ ID NO:7, encoded by SEQ ID NO:6, downstream of SEQ ID NO:1 with identity to downstream open reading frames of other cry proteins (example 7); assay of SEQ ID NO:3 for pesticidal activity against *Trichoplusa ni* (cabbage lopper) and *Tenebrio molitor* (yellow mealworm) (examples 8-11), and prophetic guidance for expression in plants (examples 12-14).

The instant specification fails to provide guidance for how to make nucleic acids encoding pesticidal protein with 90% identity to SEQ ID NO:3, 5 or 7 and nucleic acids with 90% identity to SEQ ID NO:1, 2, 4 or 6, or even towards which pests these nucleic acids would be pesticidal.

Nucleic acids encoding proteins with 90% identity to SEQ ID NO:3 or 5 would encode proteins with 69 amino acid substitutions. Nucleic acids with 90% identity to a 5980 nucleic acid like that of SEQ ID NO:1 would have 598 nucleotide substitutions, and thus encompass those that encode proteins with 598 amino acid substitutions; these proteins would have 13.7% identity to SEQ ID NO:3. Similarly, nucleic acids with 90% identity to a 2082 nucleic acid like that of SEQ ID NO:2 and a 2073 nucleic acid like that of SEQ ID NO:4 would have 208 and 207 nucleotide substitutions, respectively, thus encompassing those that encode proteins with 208 and 207 amino acid substitutions, respectively. Lastly, nucleic acids with 90% identity to a 1686 nucleic acid like that of SEQ ID NO:6 would have 168 nucleotide substitutions, thus encompassing those that encode proteins with 168 amino acid substitutions; these proteins would have 70% identity to SEQ ID NO:7.

The instant specification fails to provide sufficient guidance for which amino acids of SEQ ID NO: 3, 5 or 7 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional protein.

The guidance in the specification with respect to making amino acids substitutions in AXMI-008 is as follows:

The specification, in the paragraph starting on pg 14, line 15, says:

> Amino acid substitutions may be made in nonconserved regions that retain function. In general, such substitutions would not be made for conserved amino acid residues, or for amino acid residues residing within a conserved motif, where such residues are essential for protein activity. Examples of residues that are conserved and that may be essential for protein activity include, for example, residues that are identical between all proteins contained in the alignment of Figures 1A, B, and C or 2A and B. Examples of residues that are conserved but that may allow conservative amino acid substitutions and still retain activity include, for example, residues that have only conservative substitutions between all proteins contained in the alignment of Figures 1A, B, and C or 2A and B. However, one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues.

Conservative substitutions are defined on pg 13, line 25, to pg 14, line 2. A search of the originally filed Fig. 1, shows that there are no positions that are identical among all the proteins in the Figure, and 21 positions that have only conservative substitutions among all the proteins.

The specification on pg 13, lines 19-23 suggests that substitutions be made at amino acids that are not essential for biological activity, but does not teach any such amino acids.

The specification teaches the 4 of the 5 highly conserved regions among endotoxins in AXMI-014 (specification pg 4, lines 9-16); the regions encompass a total of 138 amino acids.

Thus, from the guidance in the specification, it would appear that the vast majority of the amino acids in SEQ ID NO:3 and 5 could be substituted.

However, although point mutations and substitutions of a few amino acids have been made in Cry proteins, no one has substituted up to 598 amino acids of a Cry protein, as encompassed the claimed nucleic acids.

Making amino acid substitutions in *cry* proteins is unpredictable. Each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1), and even conservative substitutions in nonconserved regions can have unexpected effects on protein function (Figs 2 and 3). Even a single amino acid substitution in a *cry* protein may alter its insecticidal specificity, and toxicity

must be determined empirically (Tounsi et al, 2003, J. Appl. Microbiol. 95:23-28; see pg 27, column 2, paragraph 2).

Aaronson et al (2001, FEMS Microbiol. Lett. 195:1-8) teach that there are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (paragraph spanning the columns on pg 7). de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). De Maagd et al (2001) concludes that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Thus, extensive teachings are required for making nucleic acids encoding *Cry* proteins with up to 598 amino acid substitutions relative to SEQ ID NO:3 or 5, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in *Cry* proteins by providing no working examples of proteins with up to 598 amino acid substitutions relative to AXMI-008.

The specification also suggests making the claimed nucleic acids by random mutagenesis (pg 14, line27, to pg 15, line 2). However, Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins that have up to 598 random amino acid substitutions to find those that have pesticidal

activity would require undue experimentation.

AXMI-008 has the most identity (66%) to a *cry* protein with toxicity to the dipteran mosquito (cry40Aa; see Ibarra et al, 2003, Appl. Environ. Microbiol. 69:5269-5274; abstract and Table 2). Its toxicity to Lepidopterans *T. ni* and the Coleopteran *T. molitor* suggests that AXMI-008 is a new class of *cry* toxin. Thus, given the novelty of AXMI-008 and the unpredictability making in amino acid substitutions in *cry* proteins, proteins with up to 598 amino acid substitutions relative to SEQ ID NO:3 or 5 would likely have a very different insect toxicity than AXMI-008, if such toxins could even be made. The specification does not teach the insect toxicity of such proteins. Therefore, one would not know how to use nucleic acids encoding proteins with up to 598 amino acid substitutions relative to SEQ ID NO:3 or 5.

The specification teaches that SEQ ID NO:7 has 86% identity to *cry40Aa orf2* and 85% identity to *cry39Aa orf2* and states that "these proteins also share homology to the C-terminal non-toxic domain of *cry4Aa* and *cry4Ba*" (emphasis added; pg 38, lines 9-10). Thus, one of skill in the art would not expect SEQ ID NO:7 to have any toxicity towards insects. Further, the specification does not teach how to make variants with 168 amino acid substitutions relative to SEQ ID NO:7, much less make variants with the same activity.

As the specification does not describe the transformation of any plant with a pesticidal protein with 90% identity to SEQ ID NO:3, 5 or 7, nucleic acids with 90% identity to SEQ ID NO:1, 2, 4 or 6, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with insect resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of

guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that the test is whether the necessary experimentation is routine or undue, and undue experimentation is determined by weighing the Wands factors (response pg 8-9).

This is not found persuasive because the breadth of the claims, the nature of the invention, the state of the art with respect to the knowledge of cry protein structure and function, the level of unpredictability in the art, the lack of guidance provided by the specification, the lack of working examples spanning the full scope of the claimed invention, and the quantity of experimentation all indicate that the amount of amount of experimentation require to make and use the full scope of the claimed invention would be undue.

Applicant urges that the guidance and working examples in the specification were discounted (response pg 9).

This is not found persuasive. As detailed above, the guidance is insufficient, given the scope of the claims. The working examples of SEQ ID NO:3 and its fragment SEQ ID NO:5 enables nucleic acids encoding SEQ ID NO:3 and 5, but no other working examples were provided. As detailed above, this single working example is unable to overcome the unpredictability in making the very large number of amino acid substitutions encompassed by the claims.

Applicant urges that specification provides guidance by limiting the percent identity and requiring a function; guidance is provided on pg 9-15 (response pg 9).

This is not found persuasive. Limiting the percent identity of the claimed nucleic acid

and requiring a function do not teach which amino acid substitutions may be made in the proteins. The guidance on pg 8-11 merely discusses fragment size, percent identity, and calculation of percent identity. However, guidance for determining percent identity does not teach the necessary and sufficient structural features of the claimed nucleic acids, and does not teach which amino acids could be substitutive with which other amino acids. The guidance on pg 13-14 is discussed above; it fails to sufficiently teach which amino acid substitutions to make in SEQ ID NO:3, 5 or 7, given the unpredictability in making amino acid substitutions in cry proteins.

Applicant urges that Crickmore (1998) teach that numerous δ-endotoxins were known at the time of filing; the molecular biological techniques were routine, and methods of assay are provided in the specification on pg 6 and 18-19 and Examples 8-9 and 11 (response pg 9-10).

This is not found persuasive. According to the naming system defined by Crickmore, SEQ ID NO:3's 66% identity to Cry40Aa places it in the same primary rank as the mosquito toxin cry40Aa (pg 808, left column, paragraph 2-4; Fig. 1); however, its very different insect toxicity suggests the identity relationship is deceptive. Making 208 or 598 amino acid substitutions in SEQ ID NO:3 and successfully making a functional cry protein is not taught by Crickmore or the cited portions of the specification. Further, the cited portions of the specification do not teach how to make or how to assay nucleic acids encoding proteins with 70% identity to SEQ ID NO:7.

Applicant urges that one would only need to make the claimed variants and assay them for activity using routine methods; thus the amount of experimentation is not undue (response pg 10).

This is not found persuasive. Doing so would require undue experimentation because the specification does not provide sufficient guidance as to which 598 amino acid substitutions can be made in SEQ ID NO:3. Thus, one would need to randomly make nucleic acids encoding proteins with up to 598 amino acid substitutions and test them. Because this would require trail and error experimentation and because of the likelihood of protein inactivation (see Guo et al, pg 9209, right column, paragraph 2) and the unpredictability of amino acid interactions in cry proteins (Aaronson et al, paragraph spanning the columns on pg 7; de Maagd et al, 1999, pg 4369, column 1, paragraph 1; de Maagd et al, 2001, pg 194, right column, paragraph 3), this experimentation would be undue.

Applicant urges that that Genentech states that the specification must supply the novel aspects of the invention, and in Genentech no starting materials were disclosed, while here there is a working example and guidance (response pg 10-11).

This is not found persuasive. The instant rejection is a scope of enablement rejection; the invention is enabled for nucleic acids encoding SEQ ID NO:3 and 5. The specification, however, does not provide adequate guidance for making 208 or 598 amino acid substitutions in SEQ ID NO:3 or SEQ ID NO:5 or for how to use nucleic acids encoding SEQ ID NO:7 or make nucleic acids encoding proteins with 168 amino acid substitutions relative to SEQ ID NO:7.

Applicant urges that the court also says that while every aspect of a generic claim need not be carried out, reasonable detail must be provided to enable those to carry it out (response pg 11).

This is not found persuasive because the specification fails to provide the reasonable detail for making the nucleic acids within the full scope of the claims.

Applicant urges that the specification provides a starting material and extensive description on pg 14 and Fig 1 and 2 as to which amino acid substitutions can be done (response pg 11).

This is not found persuasive. The full scope of amino acids critical to the biological activity of SEQ ID NO:3, 5 and 7 are not taught in the specification on these pages or any other. The findings and teachings of Aaronson et al, Angsuthanasombat, de Maagd et al, Tounsi et al and de Maagd et al, 2001, as well as the references cited by Applicant (Jenkins, Rajamohan, Lee, Schartz and Masson) show that interactions between amino acids in Cry proteins is much more complex than can be predicted from guidance suggesting only making conservative substitutions. De Maagd et al (2001) specifically teaches that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Applicant urges that Amgen supports the enablement of the instant invention because there is not claim to all analogs, only ones within a specific percent identity (response pg 12).

This is not found persuasive. Amgen pg 1027 says: "Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This 'disclosure' might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs." The instant specification provided no analogs of SEQ ID NO:3, 5 and 7, let alone ones with up to 598 amino acid substitutions. No similar analogs were provided in the instant case.

Applicant urges that in Lazar and Hill alteration was specifically designed to occur at highly conserved amino acids, and one of skill in the art would not be surprised that this would lead to loss of function (response pg 12-13).

This is not found persuasive. The instant specification teaches on pg 14, lines 24-26, that "one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues". Given the teachings in the specification, art directed towards the unpredictability of making substitutions in highly conserved amino acids is relevant.

Applicant urges that Jenkins and Rajamohan demonstrate that non-conservative substitutions in nonconserved regions of endotoxins resulted in a loss of activity, although Rajamohan also shows that a conservative substitution in a nonconserved region also leads to a decrease in activity (response pg 13).

This is not found persuasive. In Rajamohan 4 nonconservative substitutions resulted in a "marginally less toxic (2-3 times)" protein, while one conservative substitution and one nonconservative substitution resulted in "significantly reduced toxicity" (see abstract). In Jenkins the loss of activity in 6 nonconservative substitutions was no more than 2-fold (abstract), which is not considered significant.

Applicant urges that Lee shows that several conservative substitutions in a nonconserved region had no effect on toxicity while nonconserved substituted eliminated toxicity, and Schartz and Masson show that substitutions in conserved Group 4 amino acids decreased toxicity (response pg 13).

This is not found persuasive. In Schartz, 3 nonconservative substitutions and two conservative substitutions resulted in a less than a 2-fold decrease in toxicity (Table 1), which is not considered significant. Lee made 2 conservative substitutions and 8 nonconservative ones; only 2 of the nonconservative ones affected toxicity (pg 109, right column, paragraph 4).

Masson made eight nonconservative in 4 highly conserved arginines; of these 3 had less than a three-fold effect on toxicity (Table 1).

Although only a few conservative substitutions were analyzed in these 5 papers, about the same proportion of conservative substitutions significantly affected toxicity as did nonconservative substitutions. Conservative and nonconservative substitutions did not behave as Applicant predicts they would.

Applicant urges that the specification provides guidance regarding conservative modification in nonconserved regions that are unlikely to disrupt biological activity, as well as conserved residues unlikely to tolerate substitution; the relevance of Lazar and Hill is unexplained (response pg 13-14).

This is not found persuasive. The relevance of Lazar and Hill is that instant specification teaches on pg 14, lines 24-26, that "one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues". The instant specification does not teach that conserved residues must not be substituted, but instead suggest that they may. Lazar and Hill teach that making substitutions in highly conserved amino acids is unpredictable.

Applicant urges that if one wishes to make this many substitutions in SEQ ID NO:3, 5 or 7, the amount of experimentation is the same, regardless of the likelihood of failure, that Guo suggest inactivation is only 34%, based on data from a simple monomeric protein, and that finding many mutations in mutagenesis libraries is not surprising (response pg 14).

This is not found persuasive. The 34% inactivation probability is the probability that a single random amino acid substitution inactivates an enzyme (pg 9206, right column, paragraph

2). Guo et al did not find any isolates with more than 11 amino acid substitutions in a 298 amino acid long protein (Table 1; pg 9206, left column, paragraph 1). Whether viewed by total numbers of substitutions or by percent of total amino acids, this suggests that 208 or 598 amino acid substitutions could not be made in SEQ ID NO:3 or 5 or that 168 amino acid substitutions could not be made in SEQ ID NO:7.

Applicant urges that Li et al and Morse et al teach detailed information about the structure of δ-endotoxins, which are very well characterized; these could be used to choose among modification to retain the structure of the resultant protein without making random modifications (response pg 14-15).

This is not found persuasive. Li et al do not provide guidance for making 208 or 598 amino acid substitutions in a 693 amino acid long protein; Li et al only provided guidance for making truncations and insertion of chymotrypsin cleavage sites. Neither Li nor Morse made 208 or 598 amino acid substitutions in their proteins. Additionally, the instant specification suggests making random substitutions in SEQ ID NO:3, 5 and 7 on pg 14, lines 27-30.

It is noted that the protein taught by Li et al is a cry3Aa protein, which the instant specification teaches has only 21% identity to SEQ ID NO:2 (Table 1), and that taught by Morse et al is a cry2Aa protein, which has 10% identity to SEQ ID NO:2. This is relevant because de Maagd et al, 1999, teach that that the crystal structure of Cry1C only allows for limited prediction of the structure of Cry1Aa (pg 4373, right column, paragraph 4), which by Crickmore's nomenclature system would have between 45% and 78% identity to one another. Thus, the teachings of Li and Morse would have provide only limited guidance to one making 208 or 598 amino acid substitutions in SEQ ID NO:3.

Applicant urges that one could choose regions that are conserved among cry proteins to find modifications within the structural parameters and assay them for retention of pesticidal activity (response pg 15).

This is not found persuasive for the reasons detailed above.

Applicant urges that in de Maagd et al, 1999, several of the altered blocks map to the conserved regions, and specificity altering substitutions either occurs in conserved regions or involved non-conserved substitutions (response pg 15-16).

This is not found persuasive. The specification, in the paragraph starting on pg 14, line 15, says:

> Amino acid substitutions may be made in nonconserved regions that retain function. In general, such substitutions would not be made for conserved amino acid residues, or for amino acid residues residing within a conserved motif, where such residues are essential for protein activity. Examples of residues that are conserved and that may be essential for protein activity include, for example, residues that are identical between all proteins contained in the alignment of Figures 1A, B, and C or 2A and B. Examples of residues that are conserved but that may allow conservative amino acid substitutions and still retain activity include, for example, residues that have only conservative substitutions between all proteins contained in the alignment of Figures 1A, B, and C or 2A and B. However, one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues.

None of the residues conserved or that have only conservative substitutions among all the proteins in the instant Fig 1 were involved in the de Maagd hybrid. Additionally, the guidance in the specification teaches that substitutions may be made in all the other amino acids.

de Maagd were surprised by many of the results (pg 4373, right column, paragraphs 2-3) showing that the residues have complex and unpredictable interactions with one another or with the insect receptor.

Applicant urges that Tounsi and Angsuthanasombat discuss substitutions that were mostly nonconservative; not every conservative substitution in a nonconserved region will work, but testing them would not be undue (response pg 16).

This is not found persuasive. In Angsuthanasombat 7 nonconserved substitutions had no significant effect on activity, while 3 nonconservative and 1 conservative substitutions had a significant effect. This is completely contradictory to Applicant's insistence that substitutions conservative substitutions are fine and nonconservative ones verboten. Angsuthanasombat shows that what is actually permissible is much more complex.

Applicant urges that these references fail to support the position that the claims are not enabled (response pg 16).

This is not found persuasive. These references teach that because the interactions between amino acids in Cry proteins is much more complex than can be predicted from guidance suggesting only making conservative substitutions. The amino acids critical to SEQ ID NO:3, 5 or 7 activity are not taught, nor can they be predicted from the pre- or post-filing art.

Applicant urges that given the guidance in the specification and the knowledge in the art, the claims are enabled (response pg 16-17).

This is not found persuasive. As detailed above, the claims are not enabled within their full scope.

Applicant urges that the claims have been amended to delete reference to complementary sequences (response pg 17).

This portion of the rejection has been withdrawn.

Applicant urges that the specification establishes that SEQ ID NO:7 is a endotoxin-associated protein, and that these proteins either are toxins or act as helper or stabilizer proteins; (response pg 17).

This is not found persuasive because the specification does not teach how to assay SEQ

ID No:7 or how to make nucleic acids encoding proteins with 168 amino acid substitutions relative to SEQ ID NO:7. Further, the specification states that "these proteins also share homology to the C-terminal non-toxic domain of *cry4Aa* and *cry4Ba*" (emphasis added; pg 38, lines 9-10), which suggests that SEQ ID NO:7 is not a toxin.

Applicant urges that SEQ ID NO:7 has a high degree of similarity to other endotoxin-associated proteins, as has the conserved domains 6, 7 and 8; several of these other proteins have helper or stabilizer function, and Rosso teaches that coexpression increases toxicity (response pg 17-18).

This is not found persuasive. The specification does not teach how to assay SEQ ID NO:7 or the claimed variants or how to make them. Rosso does not make up for this deficiency.

7. Claims 1-11, 19 and 22-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 25 July 2006, as applied to claims 1-11, 19 and 22-25. Applicant's arguments filed 3 January 2007 have been fully considered but they are not persuasive.

A full review of the specification indicates that nucleic acids encoding a pesticidal protein with 95% identity to SEQ ID NO:3, 5 or 7 and nucleic acids with 95% identity to SEQ ID NO:1, 2, 4 or 6, wherein the nucleic acid encodes a pesticidal protein are essential to the operation of the claimed invention. As nucleic acids encoding proteins with 95% identity to SEQ ID NO:3, 5 or 7 would encode proteins with 35 amino acid substitutions and nucleic acids

with 95% identity to SEQ ID NO:1 encompass those that encode proteins with 299 amino acid substitutions relative to SEQ ID NO:3, 5 or 7, the claims are drawn to a broad genus of nucleic acids. The level of skill and knowledge in the art at the time of filing was such that no other proteins within the scope of the claims were known

The specification describes no relevant characteristics or motifs for the claimed nucleic acids other than identity to SEQ ID NO:1, 2, 4 or 6. At the time of filing it was known that each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1) and that even a single amino acid substitution in a *cry* protein may alter its insecticidal specificity (Tounsi et al, 2003, J. Appl. Microbiol. 95:23-28; see pg 27, column 2, paragraph 2), but the relationship between structure and pesticidal function was not known. Furthermore, the specification does not describe the structure required for the recited function, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 95% identity to SEQ ID NO:1, 2, 4 or 6 from other nucleic acids with 95% identity to SEQ ID NO:1, 2, 4 or 6 or pesticidal proteins with 95% identity to SEQ ID NO:3, 5 or 7 from other proteins with 95% identity to SEQ ID NO:3, 5 or 7.

The only species reduced to practice in the specification is SEQ ID NO:1, 2, 4 or 6, which encodes SEQ ID NO:3, 5 or 7. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1, 2, 4 or 6 alone is insufficient to describe the claimed genus.

Additionally, the only function assigned to SEQID NO:7 is "delta-endotoxin associated protein. The reference s that known proteins with identity to SEQ ID NO:7 "share homology to

the C-terminal non-toxic domain of *cry4Aa* and *cry4Ba*" (pg 38, lines 9-10) suggests SEQ ID NO:7 is not a toxin. No actual function is described.

Hence, Applicant has not, in fact, described nucleic acids encoding a pesticidal protein with 95% identity to SEQ ID NO:3, 5 or 7 and nucleic acids with 95% identity to SEQ ID NO:1, 2, 4 or 6, wherein the nucleic acid encodes a pesticidal protein, within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that the Written Description Guidelines, *Lilly* and *Enzo* state that written description requires a precise definition by structure, which is present in the 90% identity recitation (response pg 19).

This is not found persuasive. The portion of Enzo quoted by Applicant states: "the written description requirement would be met ... if the functional characteristics of [a genus of polypeptides] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Aaronson et al, de Maagd et al, 1999, and de Maagd et al, 2001, make it clear that the correlation between that function and a structure that is sufficiently known in cry proteins as a while, and the specification does not describe the motifs and amino acids required for SEQ ID NO:3, 5 or 7 biological activity.

Applicant urges that methods of assaying a determining percent identity are known in the

art and taught in the specification; further numerous other endotoxins are known in the art, and their structures studied (response pg 19-20).

This is not found persuasive because none of these describe the structure of nucleic acids encoding pesticidal proteins with 208 or 598 amino acid substitutions relative to SEQ ID NO:3 or 168 substitutions in SEQ ID NO:7.

Applicant urges that Li teaches the three-domain structure of delta-endotoxins, which provides specific structural parameters; thus, recitation of a percent identity provides defined structural parameters of the claimed sequences (response pg 20).

This is not found persuasive because this recitation does not describe the structural features responsible for the claimed function.

Applicant urges that relevant motifs were disclosed - Li teaches the 3-domain structure, each with specific functions, and conserved regions were disclosed; the 3 domain structure is generic to all delta-endotoxins and the 5 blocks are highly conserved throughout all delta-endotoxins (response pg 20-21).

This is not found persuasive. de Maagd et al, 1999, teach that that the crystal structure of Cry1C only allows for limited prediction of the structure of Cry1Aa (pg 4373, right column, paragraph 4); thus, Li's teaching is insufficient for describing the structure/function relationship of the claimed nucleic acids.

Applicant urges that a description of a representative number of species does not require individual support for each species in the genus; the representative number depends on whether one of skill in the art would recognize that Applicant was in possession of the genus; because an exemplary sequence was disclosed and because numerous delta-endotoxins were known in the

art, one of skill in the art could envision the claimed d invention (response pg 21).

This is not found persuasive. While individual support for each species is not required, support for a representative number of species is required. The specification does not describe the structure of a single nucleic acid encoding a pesticidal protein with up to 598 amino acid substitutions relative to SEQ ID NO:3.

Applicant urges that the recitation of a predictable structure is sufficient to satisfy the written description requirement (response pg 21-22).

This is not found persuasive because the correlation between structure and function is also required, but not provided by the instant specification. The relationship between structure and pesticidal function was not described in the specification.

Applicant urges that the functional limitation distinguishes the claimed genus, and the specification and art provide assays, and methods for generating variants and fragments (response pg 22).

This is not found persuasive. The specification does not describe the structure required for the recited function, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 90% identity to SEQ ID NO:1, 2, 4 or 6 from other nucleic acids with 90% identity to SEQ ID NO:1, 2, 4 or 6, pesticidal protein-encoding nucleic acids with 90% identity to SEQ ID NO:3 or 5 from other nucleic acids with 90% identity to SEQ ID NO:3 or 5, or delta-endotoxin associated protein-encoding nucleic acids with 90% identity to SEQ ID NO:7 from other nucleic acids with 90% identity to SEQ ID NO:7.

Applicant urges that the function of delta-endotoxin associated protein have been described in the art, and the specification cites references where the function is assayed, citing

Park and Ge (response pg 22).

This is not found persuasive. Park and Ge are drawn to an upstream sequences of Cry3A, Cry2A and cry 11A, which have no similarly to SEQ ID NO:7. The statement that SEQ ID NO:7 "share[s] homology to the C-terminal non-toxic domain of *cry4Aa* and *cry4Ba*" (pg 38, lines 9-10) suggests SEQ ID NO:7 is not a toxin.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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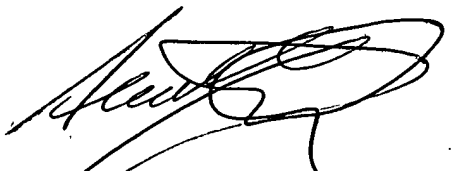
Anne Kubelik, Ph.D.
March 27, 2007



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PRIMARY EXAMINER